Tinjauan Pustaka

ADVANCING THE MANAGEMENT OF MRSA NOSOCOMIAL PNEUMONIA RESULT OF ZEPHyR TRIAL

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ABSTRACT

All MRSA infections are characterized genotypically by the presence of mecA, which encodes for altered Pen Binding Proteins (PBP's PBP2A) on their cell walls, giving rise to low affinity binding to anti-staph penicillins, resulting in phenotypically resistance to all β-lactam antibiotics, and may also contain resistant elements for numerous antibiotic classes: macrolides, lincosamides, aminoglycosides, fluoroquinolones, tetracyclines, and sulfonamides. Risk factors independently associated with MRSA infection are: Previous hospitalization within the last 12 months, late onset HAP, surgery, enteral feeding, previous antibiotics : Aminoglycoside (7.9 x), Levofloxacine (7.2 x), Macrolide (5 x), Vancomycin (4.3 x), and βL βLI (2.3 x). Most guidelines for MRSA infections support the use of Vancomycin or Linezolid if MRSA is suspected. ZEPHyR Trial is a randomized, controlled study with ratio random 1:1 from linezolid 600 mg q12h IV vs vancomycin 15 mg/kg BB IV q12h until 7-14 days, The clinical result with significancy highes for linezolid better than vancomycin, although mortality at 60 days did not show any difference. Linezolid showed overall safety and tolerability profiles were satisfactory. Summary: Indications linezolid was nosocomial pneumonia Staph aetiology both MSSA aureus / MRSA or Strep pneumoniae were sensitive to penicillin. Combination therapy when the estimated presumptive gram-negative pathogens. Dosage IV: oral 600 mg BID; pediatric dose: 10 mg/kg/8 hours. Duration of treatment 10-14 days.

Key Word : *MRSA Nosocomial Pneumonia, ZEPHyR Trial, Antibiotics*

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PENGEMBANGAN MANAJEMEN MRSA PNEUMONIA NOSOKOMIAL HASIL UJI ZEPHyR

ABSTRAK

Semua infeksi MRSA ditandai oleh genotip mecA, yang mengkode protein pengikat (PBP's, PBP2A) di dinding sel, sehingga menimbulkan penurunan afinitas dalam mengikat penisilin anti staphylococus, fenotipik ini berlaku untuk semua antibiotik gol β-lactam, dan juga dapat menjadi resisten untuk kelas antibiotik seperti: macrolides, lincosamides, aminoglycosides, fluoroquinolones, tetracyclines, and sulfonamides. Faktor risiko independen terkait dengan infeksi MRSA adalah: rawat inap 12 bulan terakhir, onset lambat dari HAP, pembedahan, makanan enteral, dan pemberian antibiotik sebelumnya: aminoglycoside (7,9x), levofloxacine (7,2x), macrolide (5x), vancomycin (4.3x), dan βL/βLI (β-lactam/β lactamase inhibitor) (2,3 x). Kebanyakan pedoman infeksi mendukung penggunaan vancomycin atau linezolid jika dicurigai MRSA. Percobaan ZEPHyR adalah suatu studi acak terkontrol dengan rasio 1:1 linezolid q12h 600 mg IV vs vancomycin 15 mg / kg BB IV q12h selama 7-14 hari, Hasil klinis bermakna lebih baik linezolid daripada vancomycin, meskipun angka kematian pada 60 hari tidak menunjukkan perbedaan. Linezolid secara keseluruhan menunjukkan keamanan dan profil tolerabilitas yang memuaskan. Ringkasan: Indikasi linezolid adalah pneumonia dengan etiologi Staphylococus aureus nosokomial baik MSSA / MRSA atau Streptococus pneumoniae yang sensitif terhadap penisilin. Kombinasi terapi diberikan bila diduga gram negatif patogen. Dosis IV sama dengan dosis oral 600 mg BID, dosis pediatrik: 10 mg/kg/8 jam. Lama pengobatan 10-14 hari.

Kata Kunci : MRSA Nosokomial Pneumonia, Uji ZEPHyR, Antibiotik

INTRODUCTION

The clinical presention of MRSA (*Methicillin Resistant Staphilococus Pneumonia*) is changing, healthy young people without the traditional risk factors for staphilococcal pneumonia are presenting with severe necrotizing infection and high mortality, most of which are methicillin resistant. All MRSA are characterized genotypicaly by the presence of mecA which encodes for altered Penicillin Binding Protein (PBP's, PBP2A) on their cell walls, resulting in low affinity binding to antistaphilococcal penicillin, causing phenotypically resistance to all β-lactam antibiotics. They may also contain resistant elements to numerous antibiotic classes such as: macrolides, lincosamines, aminoglycosides, fluoroquinolones, tetracyclines and sulfonamides.

Types of MRSA infections: 1) Hospital associated (nosocomial) MRSA infection, typically associated with invasive procedures and devices as: surgery, IV tubing, artificial joints, catheters etc, 2) Community acquired

MRSA infection, often begins as painful skin boil, spreading by skin to skin contact, forming abscesses, and can develop into life threatening infection of the blood, heart valves and lungs.

Pathogens to consider when treating HAP or VAP.

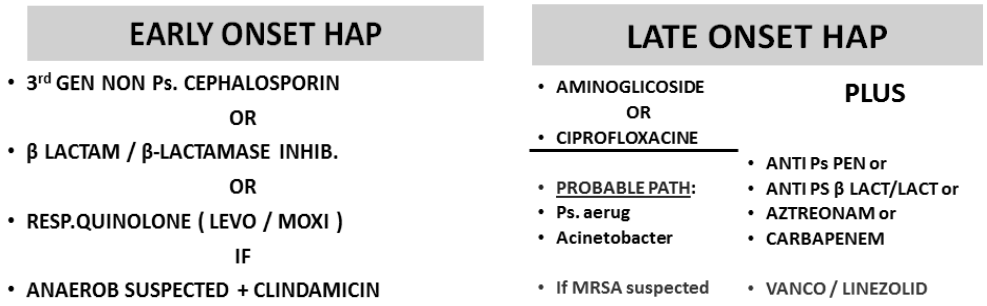
A crucial time in nosocomial pneumonia is day 5. HAP or VAP occurring before day 5 or considered early HAP or VAP and those occurring day 5 and after are classified as late HAP or VAP (picture 1).

	Early HAP/VAP	Late HAP/VAP
Timing	Within five days of admission or mechanical ventilation	Five days or more after admission or mechanical ventilation
Bacteriology	S. pneumoniae H. influenzae Methicillin-sensitive S. aureus Susceptible gram-negative bacteria	P. aeruginosa Acinetobacter MRSA Other MDR organism
Prognosis	Less severe, little impact on outcome Mortality minimal	Higher attributable mortality and morbidity

(American Thoracic Society/IDSA Am J Respir Crit Care Med 2005;171:388-416)

Figure 1. : Pathogens to Consider When Treating HAP or VAP

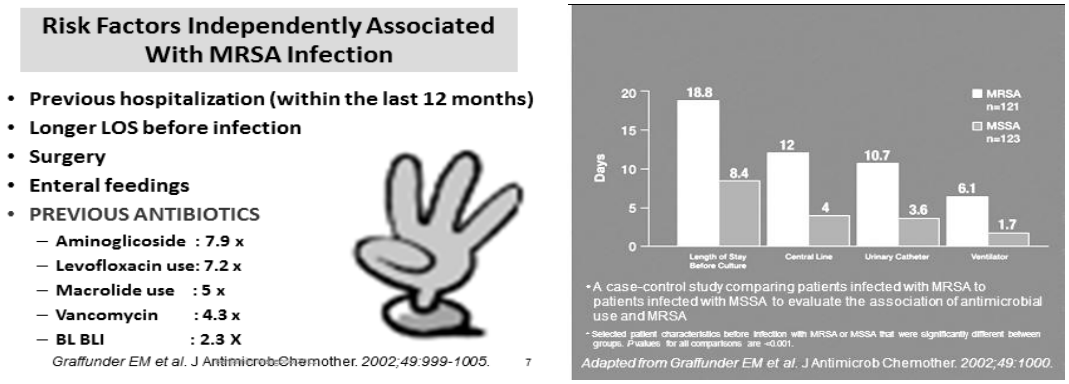
As can be seen in picture 1, MRSA is a late occurring HAP or VAP, and the antibiotic choice of therapy is either linezolid or vancomycin (picture 2).



Figur 2. : Early Onset HAP and Late Onset HAP

RISK FACTORS INDEPENDENTLY ASSOCIATED WITH MRSA INFECTION

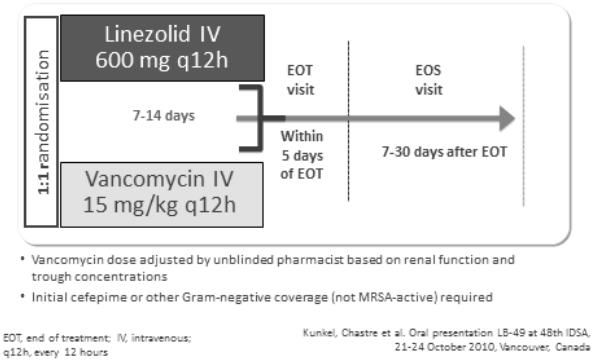
Of the risk factors independently associated with MRSA infection, the graph on picture 3 is understandable. But the list of antibiotics on table 4 is worth memorizing. Topping the list with 7.9% is aminoglycoside, followed closely by levofloxacin at 7.2%, then macrolide at 5 %.



Figur 3. : Risk Factors MRSA VS MSSA

THE ZEPHyR TRIAL

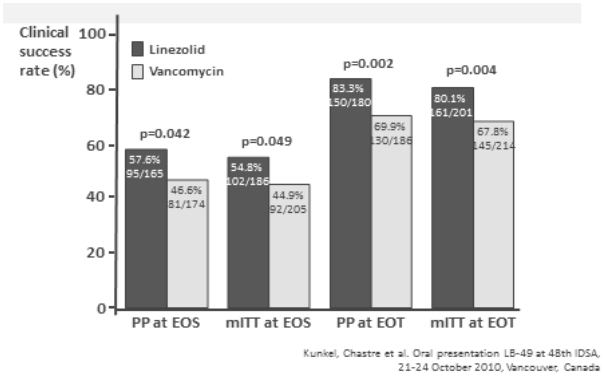
Is a linezolid vs vancomycin trial in nosocomial pneumonia. Its a randomized controlled study with a randomization ratio of 1:1. Linezolid is given at a dose of 600 mg q12h IV, while the dosage of vancomycin is 15 mg/kg BW IV q12h with a duration of therapy of 7-14 days.



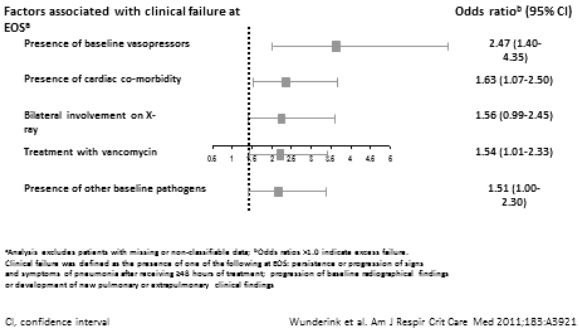
Figur 4.: Study Design ZEPHyR Trial

RESULTS

Clinical success rate of linezolid was better than vancomycin as can be seen on picture 5, although mortality at 60 days showed no difference. Several risk factors associated with clinical failure are: presence of vasopressors at baseline, presence of cardiac co-morbidity, bilateral lung involvement, previous treatment with vancomycin, and presence of other pathogens at baseline (picture 6), 100% of the MRSA isolates were susceptible to linezolid (picture 7).



Figur 5. : Clinical Success Rates Linezolid vs Vancomycin



Figur 6. : Risk Factors Associated With Clinical Failure Linezolid vs Vancomycin

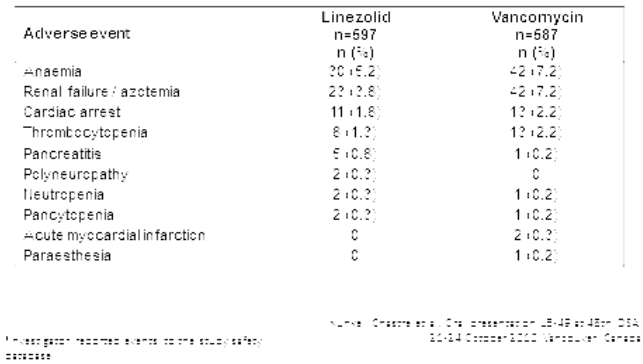
Antibiotic	MIC_{50} (mg/L)	Range (mg/L)	Susceptible (%)
Linezolid	2	1-4	100
Vancomycin	1	0.5-4	99.7
Teicoplanin	0.5	0.12->64	99.7
Erythromycin	>64	0.25->64	7
Clindamycin	>64	0.25->64	36.2
Gatifloxacin	8	0.06->16	11.7
Tetracycline	0.5	0.25->64	79.2
Trimethoprim/sulfamethoxazole	0.12	0.03-32	87.1

MIC, minimum inhibitory concentration

Hogan, Baruch. Clin Microbiol Infect 2011;17(Suppl 4):R2731

Figur 7. : 100% of The MRSA Isolates Were Susceptible to Linezolid

Noteworthy is the fact that renal failure or azotemia in the linezolid arm was almost half that of vancomycin (figur 8).



Adverse event	Linezolid n=597 n (%)	Vancomycin n=587 n (%)
Anaemia	30 (5.2)	42 (7.2)
Renal failure / azotemia	23 (3.8)	42 (7.2)
Cardiac arrest	11 (1.8)	13 (2.2)
Thrombocytopenia	8 (1.2)	13 (2.2)
Pancreatitis	5 (0.8)	1 (0.2)
Polyneuropathy	2 (0.3)	0
Neutropenia	2 (0.3)	1 (0.2)
Pancytopenia	2 (0.3)	1 (0.2)
Acute myocardial infarction	0	2 (0.3)
Paraesthesia	0	1 (0.2)

Figur 8. : Adverse Events of Interst All Causality : ITT

CONCLUSION

Conclusion of the ZEPHyR trial is that for the primary endpoint. Clinical response PP group at EOS, linezolid achieved a statistically significantly higher success rate compared to vancomycin. Similar results were observed for clinical and and microbiological response at EOS and EOT in both the PP and mITT populations. Overall, linezolid demonstrated an acceptable safety and tolerability profile for the treatment of proven MRSA nosocomial pneumonia.

Linezolid Summary : indication for nosocomial pneumonia caused by Staph.aureus (MSSA or MRSA strains) or S.pneumonia penicillin susceptible strain only), Combination therapy indicated if the documented or presumptive pathogens include gram negative organisms. Dose IV=ORAL 600 mg/bid, pediatric dose: 10 mg/kg BB/tid, duration of therapy 10-14 days.

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